REMARKS

This Amendment is filed with an RCE after Decision by the Board. By entry of this Amendment, claims 1, 4, 23, 28-38, 49-51 and 53-58 are pending; claims 28-35 and 38 are currently withdrawn from consideration. No new matter is added.

Amendments Addressing the Examiner's Rejections in the November 9, 2009 Office Action Issued Prior to Appeal

The claim amendments herein are made to address the Examiner's rejections in the Office Action issued November 9, 2009. In the Office Action the Examiner noted that Applicant argued that claim 1 comprises spray-dried solid dispersion that consists of poorly water soluble drug and HPMCAS and the drug being molecularly dispersed and amorphous in the dispersion and that the "consists of" language excludes ingredients that are not mentioned except for impurities while Miyajima makes 3- and 4-component compositions and the Kigoshi references teaches 3-component compositions rather than the two component dispersion of drug and HPMCAS Applicant claims. In response the Examiner stated: "The examiner disagrees with the appellant: a) the comprising language of the claims is open (see line 1 of claim 1) so that even though the second line of the claim uses "consists" of language, the comprising language in line 1 of the claims keeps the composition open." (Office Action paragraph 8.)

Accordingly, claim 1 has been amended to address this issue and thus, overcomes the prior rejections based on Miyajima (EP 0 344 603) and/or Kigoshi (EP 0 784 974), as neither reference teaches a two-part component dispersion as claimed and claim 1 has been amended to recite "consists of" language as well the dispersion being a homogeneous solid solution of the drug in the HPMCAS. Withdrawal of the §§ 102 and 103 rejections based on these references is respectfully requested.

New Claims:

New claim 57, which has support in paragraphs [0029], [0030], [0031], and [0033] of US Published Application Number 2002/0009494 A1, further recites that the drug of the claim 1 composition is selected from the group consisting of glycogen phosphorylase inhibitors, 5-lipoxygenase inhibitors, corticotropic releasing hormone inhibitors, griseofulvin, nifedipine, and phenytoin. For the same reasons as set forth above in regard to amended claim 1, and due to the non-enablement of the art of record as discussed below, new claim 57 is allowable.

New claim 58, which has support in paragraph [0055] in the published application, further recites that the dispersion is supersaturated in the drug. None of the art of record teaches or suggests such a spray dried solid dispersion and thus, claim 58 is allowable.

Non-enablement of Miyajima, Kigoshi and Hikosaka

Applicant recognizes that the Board, in its Decision (March 29, 2011) indicated that the Applicant needs to present evidence that Miyajima, Kigoshi, and Hikosaka are non-enabling for the making of

spray-dry dispersions as claimed (or any spray dried dispersions) as well as evidence that the references do not inherently disclose the particular claimed composition characteristics of the invented spray dried dispersions. That is, according to the Board's Decision, Applicant needs to present evidence that the references fail to inherently disclose spray dried dispersions of a drug and HPMCAS wherein, for example, the drug is molecularly dispersed in the dispersion (claim 1), the drug is amorphous in the dispersion (claim 1), the drug is homogeneous in the dispersion (claim 1), and the drug is a solid solution of drug in HPMCAS (claim 1).

The Law of Enablement in Regard to Prior Art References

In order to act as anticipating prior art, a reference (or combination of references) must enable one of ordinary skill in the art to make the invention without undue experimentation. *Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc.*, 545 F.3d 1312 (Fed. Cir. 2008). In other words, the prior art must inform as to how to make the claimed invention. *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002).

The naming of a spray dried composition in a reference, without more, cannot constitute a description of the spray dried composition and the reference is not enabling prior art. One of ordinary skill in the art must be able to make or synthesize the composition for the reference to be considered enabling prior art for the teaching of the composition. *In re Hoeksema*, 399 F.2d 269 (CCPA 1968). In *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) the court further confirmed the court's holding in *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), as reinvigorated by the Supreme Court in *KSR* (*KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007), that the cited references must contain "detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." (Emphasis added.)

Lack of Enablement of the Miyajima, Kigoshi and Hikosaka References for that which they are Cited

The Miyajima, Kigoshi and Hikosaka references all simply in passing mention that compositions might be spray dried, but none of the examples or enabled disclosed compositions are for making spray dried solid dispersions consisting of HPMCAS and a molecularly dispersed, amorphous drug in the dispersion.

i. As discussed in the record of this application, each of these references makes only a passing mention of spray drying and nothing more. None of the references give any guidance, let alone sufficient detail, for one of ordinary skill in the art to make the spray dried solid dispersion claimed by Applicant.

ii. The references do not provide sufficient information necessary to make the claimed spray dried dispersions, which require HPMCAS/drug-solution droplets be sufficiently dry enough by the time they reach a wall of a suitable spray drying apparatus that they

are essentially solid, so that they form a fine powder and do not stick to the apparatus wall, or so that the spray dried dispersion is a homogeneous solid solution with the drug being molecularly dispersed and amorphous therein. Such information needed being, in part:

- ✓ suitable solvents for a solution of drug and HPMCAS to make a spray dried dispersion
- ✓ suitable temperatures for spraying the solutions
- ✓ suitable vapor pressures of the solvents at suitable temperatures in the spray drying chambers
- ✓ suitable atmospheric total pressures in the chambers
- ✓ suitable mixing or drying gases
- ✓ suitable temperatures for the mixing or drying gases
- ✓ suitable pressures of a mixing or drying gases
- ✓ suitable temperatures and flow rates of a mixing or drying gas
- ✓ length of time needed to achieve the required level of dryness
- ✓ suitable droplet sizes
- ✓ suitable surface-to-volume ratio of the droplet
- ✓ solidification times of the drug/polymer solution
- ✓ residence time of the solid powder in the spray-drying chamber
- ✓ final solvent content of the solid dispersion as it exits the dryer and conditions necessary to achieve such solvent content
- ✓ other conditions necessary so that the particles maintain a uniform, homogeneous composition instead of separating into drug-rich and polymer-rich phases, such that the spray dried compositions are solid solutions and may be supersaturated in drug

iii. As discussed in the record of this application, none of the references teach now to make or enable making of a spray dried solid dispersion where the drug is amorphous in the dispersion.

None of the required parameters, guidance or even suggestion of the same are provided in any of the cited references and determination of the same would require undue experimentation.

Applicant understands that a further test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that the cited references satisfy the enablement requirement and whether the complex and necessary extensive experimentation is "undue."

In *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), the Court indicated that the factors to be considered when determining whether experimentation is undue include but are not limited to:

(i) The breadth of the claims;
(ii) The nature of the invention;
(iii) The state of the prior art;
(iv) The level of one of ordinary skill;
(v) The level of predictability in the art;
(vi) The amount of direction provided in the disclosure;
(vii) The existence of working examples in the disclosure; and
(viii) The quantity of experimentation needed to make the compositions based on direction provided in the disclosure.

Evidence that the Miyajima, Kigoshi and Hikosaka References are Non-Enabling to Make the Claimed Spray Dried Dispersions - the Mere Mention of the term "Spray Drying" being Insufficient to Provide the Necessary Guidance and Experimentation Necessary to do the Same Would Be Undue

Based on all of the *Wands* factors (as discussed below), Miyajima, Kigoshi and Hikosaka are not enabling and any experimentation in attempt to make the claimed spray dried compositions would be undue under the law.

(i) The breadth of the claims – Miyajima, Kigoshi and Hikosaka do not teach or suggest how to make the claimed spray dried dispersions.

(ii) The nature of the invention – none of Miyajima, Kigoshi and Hikosaka is directed to spray dried dispersions.

(iii) The state of the prior art – the prior art of record does not teach or suggest how to make the claimed spray dried dispersions; nothing provides even a hint of guidance as to any of the necessary information as set forth above.

(iv) The level of one of ordinary skill – the level of skill is that of a chemist or chemical engineer or physicist with a Bachelors of Science or higher degree.

(v) The level of predictability in the art – the level of predictability in the art is low, as the predictability of chemistry in general is low, especially in light of the fact that there is a multitude

of parameters, components and other such factors required to produce a suitable spray dried dispersion composition as claimed.

(vi) The amount of direction provided by the disclosure – there is no direction provided in any of the references cited as how to make the claimed spray dried dispersion compositions or any spray dried composition at all. This issue is discussed above.

(vii) The existence of working examples – there are no examples in the cited references showing or describing how to make the claimed spray dried dispersion compositions.

(viii) The quantity of experimentation needed based on the content of the references – spray dried dispersions require methods having a complex set of parameters, conditions and methodologies. Varying all these different parameters, conditions and methodologies, to make the claimed spray dried dispersion compositions with the desired physical characteristics, considering it from the standpoint of simple mathematics, *per se* illustrates the extensive quantity of experimentation that was required for the inventors to develop the disclosed invention.

Weighing the eight factors above, it is a fair conclusion that the cited references require undue experimentation and, thus, are not enabling for making a spray dried dispersion consisting of a sparingly water-soluble drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), said drug being molecularly dispersed and amorphous in said dispersion, having a drug:polymer weight ratio between 1:0.4 and 1:20, and said dispersion is a homogeneous solid solution of said drug in said HPMCAS.

Miyajima, Kigoshi and Hikosaka Do Not Inherently Disclose Solid Dispersions with an Amorphous Drug Therein

It has been asserted that the prior art, assuming spray dried dispersions were disclosed and enabled, inherently disclose dispersions having amorphous drugs dispersed therein. Applicant disagrees and presents the following evidence.

1. The claims require that the dispersion consist of the drug and HPMCAS, and that the drug be molecularly dispersed and amorphous in the dispersion. The cited art never describes or exemplifies how to achieve a dispersion in which the drug is molecularly dispersed and amorphous.

2. Submitted herewith is the Remington article demonstrating that materials that are spray dried can contain particles consisting of crystals and/or amorphous solids, depending on the **rate** and **conditions** of solvent removal. That is, spray drying does not necessarily and/or inherently produce amorphous drug regardless of the conditions employed.

3. The art of record fails to indicate any such conditions that would produce an amorphous solid and thus, could not properly be considered to necessarily disclose such dispersions.

4. Accordingly, the position that disclosure of spray drying would necessarily be amorphous is legally tenable only if solid amorphous spray dried dispersions are inherently (i.e., necessarily and unavoidably) produced by spray drying. However, Remington shows that solid amorphous dispersions

are not inherently produced by spray drying and the references do not provide any indication of whether its resulting dispersions include amorphous drug in an HPMCAS solid solution.

To further support the above evidence, evidence of non-enablement and lack of inherency is being submitted via a § 1.132 Declaration to be filed shortly hereafter and to be considered in conjunction with the above claim amendments and evidence.

Respectfully submitted,

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CHAPTER 37

Powders

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Powders are encountered in almost every aspect of pharmacy, both in industry and in practice. Drugs and other ingredients, when they occur in the solid state in the course of being processed into a dosage form, usually are in a more or less finely divided condition. Frequently, this is a powder whose state of subdivision is critical in determining its behavior both during processing and in the finished dosage form. Apart from their use in the manufacture of tablets, capsules, and suspensions, powders also occur as a pharmaceutical dosage form. Although the use of powders as a dosage form has declined, the properties and behavior of finely divided solid materials are of considerable importance in pharmacy.

This chapter is intended to provide an introduction to the fundamentals of powder mechanics and the primary means of powder production and handling. The relationships of the principles of powder behavior to powders as dosage forms are discussed.

PRODUCTION METHODS

Molecular Aggregation

PRECIPITATION AND CRYSTALLIZATION

The precipitation and crystallization processes are fundamentally similar and depend on achieving three conditions in succession: a state of supersaturation (super cooling in the case of crystallization from a melt), formation of nuclei, and growth of crystals or amorphous particles.

Supersaturation can be achieved by evaporation of solvent from a solution, cooling of the solution if the solute has a positive heat of solution, production of additional solute as a result of a chemical reaction, or a change in the solvent medium by addition of various soluble secondary substances. In the absence of seed crystals, significant supersaturation is required to initiate the crystallization process through formation of nuclei. A nucleus is thought to consist of from 10 to a few hundred molecules having the spatial arrangement of the crystals that will be grown ultimately from them.

Such small particles are shown by the Kelvin equation to be more soluble than large crystals; therefore, they require supersaturation, relative to large crystals, for their formation and subsequent growth. It is a gross oversimplification to assume that, for a concentration gradient of a given value, the rate of crystallization is the negative of the rate of dissolution. The latter is generally somewhat greater.

Depending on the conditions of crystallization, it is possible to control or modify the nature of the crystals obtained. When polymorphs exist, careful temperature control and seeding with the desired crystal form are often necessary. The habit or shape of a given crystal form often highly depends on impurities in solution, pH, rate of stirring, rate of cooling, and the solvent. Very rapid rates of crystallization can result in impurities being included in the crystals by entrapment.

SPRAY-DRYING

Atomization of a solution of one or more solids via a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed *spray-drying*. The nature of the powder that results is a function of several variables, including the initial solute concentration, size distribution of droplets produced, and rate of solvent removal. The weight of a given particle is determined by the volume of the droplet from which it was derived and by the solute concentration. The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal. This approach to the powdered state provides the opportunity to incorporate multiple solid substances into individual particles at a fixed composition, independent of particle size, and avoiding difficulties that can arise in attempting to obtain a uniform mixture of several powdered ingredients by other procedures.

Particle-Size Reduction

Comminution in its broadest sense is the mechanical process of reducing the size of particles or aggregates. Thus, it embraces a wide variety of operations including cutting, chopping, crushing, grinding, milling, micronizing, and trituration, which depend primarily on the type of equipment employed. The selection of equipment in turn is determined by the characteristics of the material, the initial particle size and the degree of size reduction desired. For example, very large particles may require size reduction in stages simply because the equipment required to produce the final product will not accept the initial feed, as in crushing prior to grinding. In the case of vegetable and other fibrous material, size reduction generally must be, at least initially, accomplished by cutting or chopping.

Chemical substances used in pharmaceuticals, in contrast, generally need not be subjected to either crushing or cutting operations prior to reduction to the required particle size. How-

ever, these materials do differ considerably in melting point, brittleness, hardness, and moisture content, all of which affect the ease of particle-size reduction and dictate the choice of equipment. The heat generated in mechanical grinding, in particular, presents problems with materials that tend to liquefy or stick together and with the thermolabile products that may degrade unless the heat is dissipated by use of a flowing stream of water or air. The desired particle size, shape, and size distribution also must be considered in the selection of grinding or milling equipment. For example, attrition mills tend to produce spheroidal, more free-flowing particles than do impact-type mills, which yield more irregular-shaped particles.

FRACTURE MECHANICS

Reduction of particle size through fracture requires application of mechanical stress to the material to be crushed or ground. Materials respond to stress by yielding, with consequent generation of strain. Depending on the time course of strain as a function of applied stresses, materials can be classified according to their behavior over a continuous spectrum ranging from brittle to plastic. In the case of a totally brittle substance, complete rebound would occur on release of applied stress at stresses up to the yield point, where fracture would occur. In contrast, a totally plastic material would not rebound nor would it fracture.

The vast majority of pharmaceutical solids lie somewhere between these extremes and thus possess both elastic and viscous properties. Linear and, to a lesser extent, nonlinear viscoelastic theory has been developed well to account for quantitatively and explain the simultaneous elastic and viscous deformations produced in solids by applied stresses.

The energy expended by comminution ultimately appears as surface energy associated with newly created particle surfaces, internal free energy associated with lattice changes, and as heat. Most of the energy expressed as heat is consumed in the viscoelastic deformation of particles, friction, and in imparting kinetic energy to particles. Energy is exchanged among these modes and some is, of course, effective in producing fracture. It has been estimated that 1% or less of the total mechanical energy used is associated with newly created surface or with crystal lattice imperfections.

Although the grinding process has been described mathematically, the theory of grinding has not been developed to the point where the actual performance of the grinding equipment can be predicted quantitatively. However, three fundamental laws have been advanced:

Kick's Law—The work required to reduce the size of a given quantity of material is constant for the same reduction ratio regardless of the original size of the initial material.

Rittinger's Law—The work used for particulate size reduction is directly proportional to the new surface produced.

Bond's Law—The work used to reduce the particle size is proportional to the square root of the diameter of the particles produced.

In general, however, these laws have been useful only in providing trends and qualitative information on the grinding process. Usually laboratory testing is required to evaluate the performance of particular equipment. A work index, developed from Bond's Law, is a useful way of comparing the efficiency of milling operations.[1] A grindability index, which has been developed for a number of materials, also can be used to evaluate mill performance.[2]

A number of other factors also must be considered in equipment selection. Abrasion or mill wear is an important factor in the grinding of hard materials, particularly in high-speed, close-clearance equipment (eg, hammer mills). In some instances mill wear may be so extensive as to lead to highly contaminated products and excessive maintenance costs that make the milling process uneconomical. Hardness of the material, which often is related to abrasiveness, also must be considered. This usually is measured on the Moh's scale.

Qualitatively, materials from 1 to 3 are considered as soft and from 8 to 10 as hard. Friability (ease of fracture) and fibrousness can be of equal importance in mill selection. Fibrous materials, such as plant products, require a cutting or chopping action and usually cannot be reduced in size effectively by pressure or impact techniques. A moisture content above about 5% will in most instances also create a problem and can lead to agglomeration or even liquefaction of the milled material. Hydrates often will release their water of hydration under the influence of a high-temperature milling process and thus may require cooling or low-speed processing.

METHODS AND EQUIPMENT

When a narrow particle-size distribution with a minimum of fines is desired, closed-circuit milling is advantageous. This technique combines the milling equipment with some type of classifier (see *Particle-Size Measurement and Classification*). In the simplest arrangement, a screen is used to make the separation, and the oversize particles are returned to the mill on a continuous basis while the particles of the desired size pass through the screen and out of the grinding chamber. Over-milling, with its subsequent production of fines, thereby is minimized. Equipment also has been designed to combine the sieving and milling steps into a single operation (see *Centrifugal-Impact Mills and Sieves*).

To avoid contamination or deterioration, the equipment used for pharmaceuticals should be fabricated of materials that are chemically and mechanically compatible with the substance being processed. The equipment should be easy to disassemble for cleaning to prevent cross-contamination. Dust-free operation, durability, simplified construction, and operation and suitable feed and outlet capacities are additional considerations in equipment selection.

Although there is no rigid classification of large-scale comminution equipment, it generally is divided into three broad categories based on feed and product size:

1. *Coarse crushers* (eg, jaw, gyratory, roll, and impact crushers).
2. *Intermediate grinders* (eg, rotary cutters, disk, hammer, roller, and chaser mills).
3. *Fine grinding mills* (eg, ball, rod, hammer, colloid, and fluid-energy mills; high-speed mechanical screen and centrifugal classifier).

Machines in the first category are employed ordinarily where the size of the feed material is relatively large, ranging from 1½ to 60 inches in diameter. These are used most frequently in the mineral crushing industry and will not be considered further. The machines in the second category are used for feed materials of relatively small size and provide products that fall between 20- and 200-mesh. Those in the third category produce particles, most of which will pass through a 200-mesh sieve, although often the particle size of the products from fine grinding mills is well into the micron range.

The comminution effect of any given operation can be described mathematically in terms of a matrix whose elements represent the probabilities of transformation of the various-size particles in the feed material to the particle sizes present in the output. The numerical values of the elements in the transition matrix can be determined experimentally and the matrix serves to characterize the mill. Matrices of this type are frequently a function of feed rate and feed particle-size distribution but are useful in predicting mill behavior. Multiplication of the appropriate comminution matrix with the feed-size distribution line-matrix yields the predicted output-size distribution.

INTERMEDIATE AND FINE GRINDING MILLS

The various types of comminuting equipment in this class generally employ one of three basic actions or, more commonly, a combination of these actions.